Clinical trial results:
Pharmacoepidemiology study to define the long-term safety profile of tenofovir disoproxil fumarate (Tenofovir DF, Viread®) and describe the management of Tenofovir DF-associated renal and bone toxicity in Chronic Hepatitis B (CHB)-infected adolescents aged 12 to <18 years in Europe

Summary

EudraCT number	2014-004939-39
Trial protocol	BE GB ES BG GR FR IT
Global end of trial date	11 April 2018

Results information

Result version number	v1 (current)
This version publication date	24 October 2018
First version publication date	24 October 2018

Trial information

Trial identification

Sponsor protocol code	GS-EU-174-1403

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02479880
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2018
Global end of trial reached?	Yes
Global end of trial date	11 April 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to characterize the long term (i.e., 96 weeks of follow up) bone safety profile of open-label tenofovir disoproxil fumarate (DF) treatment of adolescents with chronic hepatitis B (CHB) infection. This includes prospectively evaluating and comparing the bone mineral density (BMD) change between adolescents with CHB 12 to < 18 years of age treated with tenofovir DF in European treatment centers who are assigned to one of two schedules for renal and bone laboratory monitoring and BMD measurement. Primary study outcome will be the percent changes in BMD from Baseline through study Week 96.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.
This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 July 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	France: 3
Worldwide total number of subjects	30
EEA total number of subjects	30

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	30
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Europe. The first participant was screened on 03 July 2015. The last study visit occurred on 11 April 2018. The study did not achieve targeted enrollment as it was prematurely terminated by the Pharmacovigilance Risk Assessment Committee (PRAC).

Pre-assignment

Screening details:

35 participants were screened.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tenofovir DF + Increased Bone/Renal Monitoring

Arm description:

One 300 mg tablet given once daily for up to 96 weeks + laboratory bone biomarker testing and lumbar spine and whole-body dual-energy x-ray absorptiometry (DXA) scans every 24 weeks from baseline to Week 96 (5 scans), and monitoring of renal function at 4 and 12 weeks after baseline and every 12 weeks thereafter. With the exception of an enhanced monitoring protocol for bone and renal outcomes, participants will be managed according to local standards of care.

Arm type	Experimental
Investigational medicinal product name	Tenofovir disoproxil fumarate
Investigational medicinal product code	
Other name	Viread®, TDF
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg once daily

Arm title	Tenofovir DF + Prespecified Bone Monitoring

Arm description:

One 300 mg tablet given once daily for up to 96 weeks + laboratory bone biomarker testing and lumbar spine and whole-body DXA scans at baseline, Week 48, and Week 96. With the exception of pre-specified bone monitoring, participants will be managed according to local standards of care.

Arm type	Experimental
Investigational medicinal product name	Tenofovir disoproxil fumarate
Investigational medicinal product code	
Other name	Viread®, TDF
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg once daily

Number of subjects in period 1	Tenofovir DF + Increased Bone/Renal Monitoring	Tenofovir DF + Prespecified Bone Monitoring
Started	15	15
Completed	2	2
Not completed	13	13
Pregnancy	-	1
Study Terminated by Sponsor	13	12

Baseline characteristics

Reporting groups

Reporting group title	Tenofovir DF + Increased Bone/Renal Monitoring

Reporting group description:

One 300 mg tablet given once daily for up to 96 weeks + laboratory bone biomarker testing and lumbar spine and whole-body dual-energy x-ray absorptiometry (DXA) scans every 24 weeks from baseline to Week 96 (5 scans), and monitoring of renal function at 4 and 12 weeks after baseline and every 12 weeks thereafter. With the exception of an enhanced monitoring protocol for bone and renal outcomes, participants will be managed according to local standards of care.

Reporting group title	Tenofovir DF + Prespecified Bone Monitoring

Reporting group description:

One 300 mg tablet given once daily for up to 96 weeks + laboratory bone biomarker testing and lumbar spine and whole-body DXA scans at baseline, Week 48, and Week 96. With the exception of pre-specified bone monitoring, participants will be managed according to local standards of care.

Reporting group values	Tenofovir DF + Increased Bone/Renal Monitoring	Tenofovir DF + Prespecified Bone Monitoring	Total
Number of subjects	15	15	30
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	14	14	
standard deviation	± 1.4	± 1.5	-
Gender categorical			
Units: Subjects			
Female	5	5	10
Male	10	10	20

End points

End points reporting groups

Reporting group title	Tenofovir DF + Increased Bone/Renal Monitoring

Reporting group description:

One 300 mg tablet given once daily for up to 96 weeks + laboratory bone biomarker testing and lumbar spine and whole-body dual-energy x-ray absorptiometry (DXA) scans every 24 weeks from baseline to Week 96 (5 scans), and monitoring of renal function at 4 and 12 weeks after baseline and every 12 weeks thereafter. With the exception of an enhanced monitoring protocol for bone and renal outcomes, participants will be managed according to local standards of care.

Reporting group title	Tenofovir DF + Prespecified Bone Monitoring

Reporting group description:

One 300 mg tablet given once daily for up to 96 weeks + laboratory bone biomarker testing and lumbar spine and whole-body DXA scans at baseline, Week 48, and Week 96. With the exception of pre-specified bone monitoring, participants will be managed according to local standards of care.

Primary: Percentage of Participants with Bone-Related Adverse Events and/or a ≥ 4% Reduction in BMD from Baseline to Week 96

End point title	Percentage of Participants with Bone-Related Adverse Events and/or a ≥ 4% Reduction in BMD from Baseline to Week 96[1]

End point description:

Participants in the Safety Analysis Set (participants who were randomized into the study and received at least one dose of Viread) with available data were analyzed.

End point type	Primary

End point timeframe:

Week 96

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Because this study did not achieve targeted enrollment as it was prematurely terminated by the PRAC, the statistical analysis for this endpoint was not performed.

End point values	Tenofovir DF + Increased Bone/Renal Monitoring	Tenofovir DF + Prespecified Bone Monitoring		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: percentage of participants				
number (not applicable)	6.7	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

96 weeks + 30 days

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Tenofovir DF + Increased Bone/Renal Monitoring

Reporting group description:

One 300 mg tablet given once daily for up to 96 weeks + laboratory bone biomarker testing and lumbar spine and whole-body DXA scans every 24 weeks from baseline to Week 96 (5 scans), and monitoring of renal function at 4 and 12 weeks after baseline and every 12 weeks thereafter. With the exception of an enhanced monitoring protocol for bone and renal outcomes, participants will be managed according to local standards of care.

Reporting group title	Tenofovir DF + Prespecified Bone Monitoring

Reporting group description:

One 300 mg tablet given once daily for up to 96 weeks + laboratory bone biomarker testing and lumbar spine and whole-body DXA scans at baseline, Week 48, and Week 96. With the exception of pre-specified bone monitoring, participants will be managed according to local standards of care.

Serious adverse events	Tenofovir DF + Increased Bone/Renal Monitoring	Tenofovir DF + Prespecified Bone Monitoring	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 15 (6.67%)	2 / 15 (13.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Calcinosis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			

subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Tenofovir DF + Increased Bone/Renal Monitoring	Tenofovir DF + Prespecified Bone Monitoring	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 15 (66.67%)	10 / 15 (66.67%)	
Investigations			
Vitamin D decreased			
subjects affected / exposed	2 / 15 (13.33%)	2 / 15 (13.33%)	
occurrences (all)	4	3	
Bone density decreased			
subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Somnolence			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Tremor			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 15 (6.67%)	2 / 15 (13.33%)	
occurrences (all)	2	2	
Vomiting			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Abdominal pain lower			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Anal fissure			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Dyschezia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Food poisoning			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Nausea			

subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Dyspareunia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Muscle contracture			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Pharyngitis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Ear infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Otitis media			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Viral infection			

subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Metabolism and nutrition disorders Vitamin D deficiency subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1	 0 / 15 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 February 2015	Serum renal chemistry (i.e., glucose, creatinine, calculated creatinine clearance): at 4 weeks and 12 weeks from Baseline and every 12 weeks thereafter [changed from every 4 weeks from Baseline to Week 48 and every 12 weeks thereafter]. Urinalysis (i.e., protein, glucose, creatinine, phosphate, bicarbonate, blood): at 4 weeks and 12 weeks from Baseline and every 12 weeks thereafter [changed from every 4 weeks from Baseline to Week 48 and every 12 weeks thereafter]. Clarification of pregnancy screening (after Baseline) as a urine screen wherever referenced. Clarification to recommend a fasted state for collecting serum renal chemistry and urinalysis, serum bone chemistry. Clarification that DXA should be performed +/- 14 days from the scheduled clinic visit.
10 March 2015	Revised reference to the study drug through out the protocol. Changed from 245 mg tenofovir disoproxil to 300 mg tenofovir disoproxil fumarate, tenofovir DF (Viread®), which is equivalent to 245 mg tenofovir disoproxil.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported